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Clinical correlation between hypercoagulability and thrombo-embolic phenomena

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Clinical correlation between hypercoagulability and thrombo-embolic phenomena. A study of the coagulolytic balance as well as platelet aggregation was carried out in 64 nephrotic patients. The data were correlated, in a prospective attempt, with the clinical demonstration of thrombo-embolic events. Activating factors (factors I, VIIIc, VIIIr:Ag) were increased as well as certain clotting inhibitors, α-1-antitrypsin and α-2-macroglobulin. There was a platelet hyperaggregability in 31.5% of our patients. Thrombo-embolic complications occured in six subjects (9%). The data of these six patients were compared with that of the others patients; no significant correlation were found between clotting abnormalities and thrombosis. Low level of AT_{III} (<0.8 U.Fr) and severe hypoalbuminemia (<20 g/liter) were of no predictive value for the occurrence of thrombo-embolic events.

The incidence of thrombo-embolic complications in patients with nephrotic syndrome varies between 8% and 33% [1]. In our experience, at the time of a retrospective study covering a ten year period, we noted 267 patients with nephrotic syndrome. The incidence of thrombo-embolic events in this series was 4%.

The occurrence of these complications could be favored by a disequilibrium of the coagulo-lytic balance, which is characterized by an increase of activating proteins (factors I, V, VII) and a decrease of certain clotting inhibitors (AT_{III}) associated with a platelet hyperaggregability. Data from the literature concerning these abnormalities are fragmented, focusing either on the activating system, or the inhibiting system, or upon platelet aggregation.

This led us to carry out a prospective study of the clotting activators and inhibitors of the coagulolytic system as well as an evaluation of platelet aggregation in 64 nephrotic patients. The main aims of the study were: a) to establish an overall profile of coagulation and platelet abnormalities and their relationship to hypoalbuminemia, proteinuria and blood cholesterol; b) to compare the level of coagulation of nephrotic patients having thrombo-embolic complications with nephrotic patients free from thrombotic complications; and c) to evaluate the relationship between the clinical profile of these 64 patients (such as presence or absence of thrombotic complications) and their coagulation blood abnormalities.

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Methods

The 64 patients selected for the study had a serum albumin less than 30 g/liter and protein excretion was greater than 3 g/24 hours. The mean age was 47 ± 19 years and there were 32 females (mean age 45 ± 20 years) and 32 males (mean age 48 ± 18 years).

The nephrotic syndrome was primary in 36 patients and secondary in 28 patients. Eighteen patients had nephrotic syndrome without any other renal manifestations, while the remaining 46 patients had hematuria and/or hypertension and/or renal failure. Thrombo-embolic complications were observed in six patients.

In order to correlate the relationship between the clinical profile and coagulation abnormalities, the patients were distributed into two groups: group I were nephrotic patients with thrombo-embolic complications (N = 6); and group II comprised nephrotic patients without thrombo-embolic complications (N = 58). To obtain additional correlations, we stratified the 64 patients according to the level of AT_{III} and the serum level of albumin. Patients with a low level of AT_{III} (< 0.8 U.Fr) and patients with severe hypoalbuminemia (<20 g/liter) were biologically considered at high thrombogenic risk; they were respectively compared with patients having normal level of AT_{III} and patients having hypoalbuminemia >20 g/liter. The frequency of thrombo-embolic events was assessed in each group in order to correlate biological data with thrombotic complications. Finally the patients were subdivided into two groups according to the presence or absence of a membranous nephropathy. Laboratory data and evidence of thrombo-embolic events were also compared.

A transcutaneous renal biopsy was performed in 61 patients. No drug had been previously administered. Blood samples were taken in the morning in fasting patients without prolonged venostasis. Platelet–count was performed by a Coulter Counter (S + 2) (N = 250,000 ± 50,000) (Coulter Electronics, Hialeah, Florida, USA); platelet aggregability was evaluated according to the Born, Cross method [2]; fibrinogen assay was done by the technique of Von Clauss [3] (N = 300 ± 50 mg/dl); the prothrombin time was measured using Stago calcic anti-heparin thromboplastin (N = 1 ± 0.2 U.Fr). Factor VIII coagulant was determined according to the technique of Diagnostica Stago (N = 1 ± 0.2 U.Fr); factor VIII antigenic (VIIIr:Ag) was measured

Table 1. Distribution of histological lesions (61 patients)

Histology	Min. ch.	Memb.	Amyl.	Foc. scler	ANS	Preecl.	Mesang. prolif.	Memb.	Diabete K.W.	Acute GN
Number of cases	11	9	8	6	6	5	5	4	4	3

Abbreviations are: Min. ch. (minimal change); Memb. (membranous); Amyl. (amyloidosis); Foc. scler. (focal sclerosis); ANS (arterio-nephrosclerosis); Preecl. (pre-eclampsia); Mesang. (mesangial); Memb. prolif. (membrano-proliferative); K.W. (Kimmelstiel-Wilson); Acute GN (acute glomerulonephritis).

Table 2. Coagulation parameters for all 64 patients, Mean ± SD

Unit	VIIIc	VIIIr:Ag	P.T.	Fib.	C3	Plat.	Plg	α-2AP	α-2MA	α-1AT	C1I	AT_{III}	Chol.
	U.Fr.			*mg/dl*		*giga/liter*	*U.Fr.*		*mg/dl*			*U.Fr.*	*mmol/liter*
Normal value	1	1	1	300	170	250	1	1	200	190	20	1	5.2
	±0.2	±0.2	±0.2	±50	±70	±50	±0.2	±0.2	±100	±60	±8	±0.2	±1.2
Patients mean SD	1.35[c]	2.75[c]	0.98	680[c]	121[c]	342[b]	1	0.98	366[c]	218[a]	22	0.95	7.5[c]
	±0.38	±1.38	±0.2	±260	±40	±144	±0.25	±0.23	±162	±93	±8	±0.26	±2.9

Abbreviations are: factor VIII coagulant (VIIIc); factor VIII related antigen (VIIIr:Ag); prothrombin time (P.T.); plasminogen (Plg); α-2-antiplasmin (α-2AP); antithrombin III (AT_{III}); unit fraction (U.Fr); fibrinogen (Fib.); third component of complement (C 3); α-2-macroglobulin (α-2-MA); α-1-antitrypsin (α-1-AT); C1 inhibitor (C1I); cholesterol (chol.)

[a] $P < 0.05$
[b] $P < 0.01$
[c] $P < 0.001$

by a laser nephelometry (N = 1 ± 0.2 U.Fr) [4]; assay of fraction 3 of the complement was made by radial immunodiffusion (N = 170 ± 70 mg/dl) (Partigen–Behring); the Kabi-Vitrum chromogenic technique was used for the dosage of α-2-antiplasmin (N = 1 ± 0.2 U.Fr); the Diagnostica Stago chromogenic technique was used for the dosage of α-2-macroglobulin (N = 200 ± 100 mg/dl), α-1-antitrypsin (N = 190 ± 60 mg/dl), C1 inhibitor (N = 20 ± 8 mg/dl); antithrombin III (AT_{III}) (N = 1 ± 0.2 U.Fr) and of plasminogen (N = 1 ± 0.2 U.Fr).

Statistical analysis of the results are comprised of comparisons of the averages of the results according to Student's t-test, and correlation tests following a linear regression, as well as χ^2 test with YATES correction.

Results

Histological lesions are detailed in Table 1. The clotting profile of 64 patients is represented in Table 2. Most of the activating clotting factors were significantly increased when compared to normal: fibrinogen (680 ± 260 mg/dl); factor VIIIC (1.35 ± 0.38 U.Fr), and factor VIIIr:Ag (2.75 ± 1.38 U.Fr). Fraction 3 of the complement was significantly decreased to 121 ± 49 mg/dl). For clotting inhibitors, we noted an increase of α-2-macroglobulin to 366 ± 166 mg/dl and of α-1-antitrypsin to 218 ± 93 mg/dl, while C1 inhibitors α-2-antiplasmin and AT_{III} remain within the normal range.

There was a significant increase in the number of platelets to 342,000 ± 144,000. The study of their aggregability performed in 51 patients revealed 31.5% of hyperaggregability, 31.5% of hypoaggregability and 37% of normal aggregation. As shown in Table 3 there was a platelet hypersensitivity to low doses of ADP (0.5 γ) while their reactivity is normal with larger doses of ADP (1.25 and 2.5 γ). The platelet response to collagen was normal.

Table 3. Platelet aggregability to various doses of ADP and to collagen

	ADP			Collagen	Platelet count
	0.5 γ	1.25 γ	2.5 γ		
Normal	15.1% ± 0.59%	38.9% ± 1.03%	52.5% ± 0.49%	54.31% ± 0.67%	250 000 ± 50 000
Patients	30.8% ± 4.1%[a]	38.8% ± 3.7%	46.6% ± 3.92%	49.34% ± 2.6%	342 000 ± 142 000[b]

[a] $P < 0.001$
[b] $P < 0.01$

Comparison of the results according to the existence or the absence of a thrombo-embolic complication

The group of six patients who presented a thrombo-embolic complication (group I) was compared to the group of 58 patients free from complication (group II). The only significant difference (Table 4) concerns C1I which was increased to 31.6 mg/dl in group I, while it was 21.6 mg/dl in group II. The magnitude of the hypoalbuminemia and proteinuria did not differ significantly in the two groups; the mean albuminemia was 18.8 ± 4.7 g/l and the mean proteinuria was 11.2 ± 5 g/24 hours in group I, whereas the mean values were 21.2 ± 5.1 g/liter and 8.8 ± 6 g/24 hours, respectively, in group II. The clinical and clotting profiles of the six thrombotic patients are described in detail in Tables 5 and 6. We noted a predominance of membranous

Table 4. Coagulation parameters: patients with thrombo-embolic events (group I $N = 6$) versus patients without thrombo-embolic events (group II $N = 58$), mean ± SD

Unit	VIIIc	VIIIr:Ag	P.T.	Fib.	C3	Plat.	Plg	α-2AP	α-2MA	α-1AT	C1I	AT_{III}	Chol.
	U.Fr.			*mg/dl*		*giga/liter*	*U.Fr.*		*mg/dl*			*U.Fr.*	*mmol/liter*
Group I	1.21	2.35	0.98	533	106	316	0.92	0.88	369	220	31	0.86	6.39
	±0.4	±1.54	±0.23	±176	±64	±63	±0.28	±0.16	±221	±69	±13[a]	±0.21	±3.03
Group II	1.35	2.75	0.99	670	123	369	1.02	0.98	366	218	21	0.95	7.46
	±0.4	±1.4	±0.21	±260	±48	±160	±0.25	±0.24	±160	±94	±7	±0.27	±1.08

[a] $P < 0.01$

Table 5. Clinical and clotting profile of the six thrombotic patients

Case	Histology	S.Alb.	Prot U/day	Thrombosis	VIIIc	VIIIr:Ag	Fib.	Plat.	Plg.	α-2AP	α-2MA	α-1AT	C1I	AT_{III}	Plat. Aggr
1	Nephro-sclerosis	19.7	3	bilateral popliteal thrombosis	1.16	2.85	474	225	0.77	.7	214	238	49	0.9	Not done
2	Membrano-proliferative	20	3.2	left iliofemoral	1.2	1.97	570	421	1.2	1.12	234	155	38	1	Hyper
3	Membranous	19	24	left renal vein	1.2	0.9	474	370	1.25	0.75	476	260	34	0.99	Hyper
4	Membranous	12	6	Right and left renal veins	1.3	4.6	1002	290	.68	0.90	213	305	12	0.9	Not done
5	Mesangial	11	20	left arterial embolism	1.2	0.95	810	435	.72	0.92	712	142	25	0.42	Hyper
6	Membranous	14	3.5	Right popliteal	2.12	2.9	840	350	.95	0.25	382	252	50	0.8	Normal

Table 6. Predisposing factors and evolution of the six thrombotic patients

Case	Predisposing factor	Delay	Evolution of thrombosis	Evolution of nephro. synd.	Histology
1	Cardiac failure, long term diuretic therapy (30 days)	30 days	favorable	C.R.F. hemodialysis in 7 months	nephrosclerosis
2	Long term diuretic therapy (30 days)	30 days	favorable	C.R.F. hemodialysis in 16 months	membranous proliferation
3	Membranous nephropathy	Discovered during the first hospitalization	favorable	Disappearance by steroid therapy. Mild proteinuria (0.3 g|24 hrs) 2 years after the onset of the disease	membranous
4	Long term diuretic therapy (60 days). Membranous nephropathy	60 days	favorable	Spontaneous regression persistent proteinuria (1g/24 hrs) 4 years after the onset of the disease	membranous
5	Long term diuretic therapy (60 days). Diarrhoea, extracellular dehydration	90 days	Amputation of the left leg	Patients died after surgery	mesangial G.N.
6	Membranous nephropathy	15 months	favorable	Nephro, synd. persistent until the thrombotic complication, then regression, persistent mild proteinuria (0.40g|24 hrs)	membranous

nephropathy (3 patients). Platelet hyperaggregability was noted in three out of the four cases explored.

Thrombogenic risk, albuminemia and AT_{III}

The thrombogenic risk factors during nephrotic syndrome, such as hypoalbuminemia <20 g/liter and decreased level of AT_{III} (<0.8 U.Fr), [5–7] were evaluated.

The comparison of coagulation parameters of patients having hypoalbuminemia <20 g/liter with those of patients having hypoalbuminemia >20 g/liter (Table 7) revealed a significant difference for fibrinogen, α-2-macroglobulin and cholesterol which were inversely correlated with the severity of hypoalbuminemia. Platelet aggregation was increased in 38% of the patients with hypoalbuminemia <20 g/liter, whereas it was increased in only 15% of patients with hypoalbuminemia >20

Table 7. Coagulation parameters: patients with hypoalbuminemia < 20 g/liter ($N = 29$) versus patients with hypoalbuminemia > 20 g/liter ($N = 35$), mean ± SD

Unit	VIIIc	VIIIr:Ag	P.T.	Fib.	C3	Plat.	Plg	α-2AP	α-2MA	α-1AT	C1I	AT_{III}	Chol.
	U.Fr.			*mg/dl*		*giga/liter*	*U.Fr.*		*mg/dl*			*U.Fr.*	*mmol/liter*
ALB < 20 g/liter	1.37	2.39	0.99	842	120	368	0.95	0.99	425	207	22	0.88	8.87
	±0.41	±1.42	±0.17	±274[b]	±41	±106	±0.25	±0.23	±180[a]	±105	±10	±0.13	±3.08[b]
ALB > 20 g/liter	1.36	2.99	0.98	559	115	316	1.04	0.99	316	232	21	1	6.48
	±0.44	±1.28	±0.16	±184	±46	±164	±0.24	±0.24	±128	±86	±6.61	±0.18	±2.01

[a] $P < 0.05$
[b] $P < 0.01$

Table 8. Coagulation parameters: patients with low AT_{III} levels ($N = 11$) versus patients with normal AT_{III} ($N = 53$), mean ± SD

Unit	VIIIc	VIIIr:Ag	P.T.	Fib.	C3	Plat.	Plg	α-2AP	α-2MA	α-1AT	C1I	AT_{III}	Chol.
		U.Fr.		*mg/dl*		*giga/liter*	*U.Fr.*		*mg/dl*			*U.Fr.*	*mmol/liter*
AT_{III}	1.19	2.49	0.98	713	110	400	0.73	0.83	381	183	20.3	0.63	9.31
< 0.8	±0.22	±1.34	±0.19	±252	±69	±249	±0.15[b]	±0.24[a]	±186	±62	±5.2	±0.12[b]	±4.19[a]
AT_{III}	1.36	2.8	1	670	123	335	1.06	1	365	227	22.5	1.02	7.25
> 0.8	±0.39	±1.4	±0.2	±270	±50	±114	±0.23	±0.24	±156	±99	±8.3	±.24	±2.37

[a] $P < 0.05$
[b] $P < 0.001$

Table 9. Coagulation parameters: patients with membranous nephropathy ($N = 9$) versus patients without membranous nephropathy ($N = 55$), mean ± SD

Unit	VIIIc	VIIIr:Ag	P.T.	Fib.	C3	Plat.	Plg	α-2AP	α-2MA	α-1AT	C1I	AT_{III}	Chol.
		U.Fr.		*mg/dl*		*giga/liter*	*U.Fr.*		*mg/dl*			*U.Fr.*	*mmol/liter*
Memb. n.	1.39	2.06	0.99	707	141	294	1.02	0.86	369	205	28	1.02	8.62
	±0.37	±1.06	±0.18	±179	±45	±118	±0.22	±0.32	±109	±74	±10[a]	±0.22	±2.76
Others	1.35	2.75	0.98	680	119	352	1	0.99	368	223	21	0.94	7.28
	±0.38	±1.38	±0.12	±280	±45	±149	±0.26	±0.21	±170	±98	±7[a]	±0.25	±2.36

[a] $P < 0.05$

g/liter. However, the incidence of thrombo-embolic complications was the same in both groups.

When coagulation parameters of patients with low AT_{III} level (<0.8 U.Fr) were compared with those of patients with normal AT_{III} level, significant decrease of plasminogen and α-2-antiplasmin was noted in the former group (Table 8). Patients with low AT_{III} level had more severe hypoalbuminemia (17 ± 4 g/liter versus 22 ± g/liter, $P < 0.05$) and greater proteinuria (12 ± 6.7 g/24 hrs versus 6.9 ± 5 g/24 hrs, NS) than patients with normal AT_{III} level. Platelet hyperaggregability and the incidence of thrombo-embolic events were similar in both groups.

Thrombogenic risk and membranous nephropathy

When a comparison was made between nephrotic syndrome secondary to membranous nephropathy and nephrotic syndrome due to other histological lesions, the only difference concerns C1I (Table 9). Platelet hyperaggregability was noted in 55% of patients with membranous nephropathy and in 20% of patients with other histological lesions. Despite the absence of difference in coagulation data between both groups (platelet aggregability excepted) there was a large predominance of thrombotic complications in patients with membranous nephropathy (33%). The incidence of such complications was only 6% in patients with other glomerulopathy.

Longitudinal study

The mean duration of the following up of the patients was 21.2 ± 14 months with extreme ranges from 1 to 48 months. Six patients died: two were diabetics, two were afflicted by amyloidosis, one had membranous nephropathy, and one membrano-proliferative glomerulonephritis. Out of these six patients, one presented a thrombo-embolic complication (case 5, Table 5), and he died in the immediate post-embolic period.

Five of the coagulation complications observed, occurred early with respect to the apparent onset of the nephrotic syndrome (between 15 and 90 days, Table 6). Samples for the coagulation study were collected just before the occurrence of thrombosis. In one case (case 6 in Table 6) thrombosis appeared after an evolution of 15 months. The results of the coagulation study during the first hospitalization and at the time of the thrombotic event are given in Table 10.

No significant modification was observed, and in particular AT_{III} was normal at the time of the thrombotic event. Severe hypoalbuminemia was persistent. In the other patients, no thrombotic complication was observed and the successive coagulation studies realised in the course of the nephrotic syndrome remained unchanged. We noted a rapid normalization of the disorders when the nephrotic syndrome disappeared.

Table 10. Coagulation data during the first hospitalization and at the time of the thrombotic complication

	December 1981	March 1983
Alb. S	14 g/liter	17 g/liter
Fib.	770 mg/dl	710 mg/dl
VIIIc	2.12 U.Fr	1.9 U.Fr
VIIIr:Ag	2.9 U.Fr	4 U.Fr
α-2-MA	309 mg/dl	267 mg/dl
α-2-AP	0.60 U.Fr	0.95 U.Fr
α-1-AT	185 mg/dl	169 mg/dl
Plg	0.9 U.Fr	1 U.Fr
C1I	24 mg/dl	18 mg/dl
AT_{III}	0.8 U.Fr	0.93 U.Fr
Platelet Aggregation	Hyper	Not done

Discussion

The increase of the specific proteins [8, 9] of the intrinsic system, such as fibrinogen, prothrombin and factor VIII complex, observed in the present study is in agreement with previous observations [9, 10]. In this study the mean plasma fibrinogen level was more than twice the normal value. There was a significant inverse relation between fibrinogen and albuminemia ($P < 0.001$) and a significant correlation between fibrinogen and blood cholesterol level ($P < 0.001$). High level of plasma fibrinogen increases blood viscosity and it is an important factor in the prethrombotic state of the nephrotic syndrome. Nevertheless, in our study fibrinogen level was of no value for the prediction of a thrombo-embolic complication (Table 4).

Urinary losses of factors VIIIc and VIIIr:Ag do not occur because of their high molecular weight. The increase of factor VIIIr:Ag was more significant than that of factor VIIIc. In contrast to some authors [11], we observed no correlations between factor VIIIc and VIIIr:Ag. These two proteins were of no predictive value for the occurrence of thrombo-embolic complications (Table 4). Their plasma levels were higher in patients without thrombotic complications than in patients with such complications.

A disequilibrium between the clotting activator system and the inhibitor system may be important in the hypercoagulability of nephrotic syndrome. Thus, urinary losses of small molecular weight inhibitors, AT_{III} and α-1-AT have been observed [12, 13]. In the 64 patients of the present study, we noted an inverse correlation between proteinuria and AT_{III} ($P < 0.05$) and between proteinuria and α-1-AT ($P < 0.05$). There was a positive correlation between the levels of serum albumin and AT_{III} ($P < 0.01$). This is concordant with previous observations relating a decrease of AT_{III} to serum albumin levels [8]. However, among the eleven patients with low AT_{III} levels (< 0.8), only one thrombotic episode was observed. Thus in the present study the decrease of AT_{III} was not a good index of the risk of thrombosis. This is in agreement with the studies of Wagonner et al [14] whose patients with renal vein thrombosis have been found to have normal levels of AT_{III}.

A defect of fibrinolysis may also be important in the hypercoagulability and the occurrence of thrombosis in the nephrotic syndrome. In this study plasminogen levels were normal in all 64 patients. However in patients with low AT_{III} levels (Table 8), plasminogen levels were significantly reduced and there was a positive correlation between AT_{III} and plasminogen ($P < 0.01$). Despite the important abnormalities of the activator–inhibitor system observed in these eleven patients, the incidence of the coagulation complications was not different from that observed in the other patients. Moreover, mean plasminogen and AT_{III} levels are within the normal range in the six thrombotic patients (Table 4).

Platelet hyperaggregability may also be considered as a thrombogenic risk factor. We observed platelet hyperaggregability in 16 patients, and in seven of them spontaneous aggregation occurred. Evaluation of platelet aggregation induced by collagen and ADP demonstrated a normal platelet response to collagen while it was increased by low doses of ADP (0.5 γ) and returned to normal with larger doses (1.25 γ and 2.5 γ). This hypersensitivity of platelets to low doses of ADP has been previously reported [8, 15]. Two proposed mechanisms may be responsible for this response: hypercholesterolemia and hypoalbuminemia [8, 16–18]. In this study the patients with hyperaggregability had a lower serum albumin and a higher serum cholesterol than the patients with a normal platelet aggregability, but the differences were not significant. The incidence of thrombotic complications is 18.75% (three of 16) in patients with hyperaggregability, versus 8.5% (three of 35) in patients with normo- or hypoaggregability. These percentages are not significantly different (χ^2 test with Yates correction).

Five patients had three cumulative risk factors: hypoalbuminia <20 g/liter, $AT_{III} < 0.8$ U.Fr, platelet hyperaggregability; none of them presented a thrombo-embolic event during the follow-up of this study.

Finally, clotting activators and inhibitors do not seem to be of predictive value for thrombogenic risk. Considering our results, the most important predictive factor is the existence of a membranous nephropathy as 33% of the patients having this histological lesion presented a thrombo-embolic complication, and among the patients with thrombosis, 50% had membranous nephropathy (Table 5). When we compare the clotting data of thrombotic patients with that of non-thrombotic patients, no significant difference emerges, save for C_1I whose role as inhibiting factor is minor. Thus it seems to us that nephrotic syndrome may be considered generally as a hypercoagulable state in which thrombotic events are started by additional clinical events or therapy. We looked for the clinical manifestations or therapy which could have increased blood viscosity in our patients. We noted that four out of the six thrombotic subjects had long-term diuretic therapy (Table 6), one of them having an additional clinical factor of dehydration (case 5). None of the non-thrombotic patients received long-term diuretic therapy. Thus, we believe that the induction of hypovolemia in nephrotic syndrome may increase the blood hyperviscosity and add to the risk of thrombosis.

A prospective study may be necessary to assess the role of long-term diuretic therapy in nephrotic patients.

In conclusion, it seems important to emphasize the incidence of thrombo-embolic events (9%) in our series of 64 patients and to underline the absence of parallelism between thrombo-embolic complications and specific clotting abnormalities. Thus, no clotting criterium is predictable for the occurrence of

thrombo-embolic complications. The evidence of blood hyperviscosity in nephrotic syndrome is convincing. Circulating conditions may play a preponderant role in the modifications of blood coagulation.

Efforts should be made to develop therapeutic measures to prevent hemodynamic abnormalities (diuretic therapy probably represents an enhanced risk factor in these patients) and to combat blood hyperviscosity. Membranous nephropathy is associated with a high incidence of thrombotic complications, but no biological factor is able to predict the onset of thrombosis.

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